**ANNEX I**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Xtandi 40 mg soft capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 40 mg of enzalutamide.

Excipient with known effect:
Each soft capsule contains 52.4 mg of sorbitol.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Soft capsule.
White to off-white oblong soft capsules (approximately 20 mm x 9 mm) imprinted with “ENZ” in black ink on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Xtandi is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

### 4.2 Posology and method of administration

Posology
The recommended dose is 160 mg enzalutamide (four 40 mg capsules) as a single oral daily dose.

If a patient misses taking Xtandi at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.

*Concomitant use with strong CYP2C8 inhibitors*
The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor (see section 4.5).

*Older people*
No dose adjustment is necessary for older people (see section 5.2).

*Hepatic impairment*
No dose adjustment is necessary for patients with mild hepatic impairment (Child Pugh Class A). Caution is advised in patients with moderate hepatic impairment (Child Pugh Class B). Xtandi is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) (see section 4.4 and 5.2).

*Renal impairment*
No dose adjustment is necessary for patients with mild or moderate renal impairment (see section 5.2). Caution is advised in patients with severe renal impairment or end-stage renal disease (see section 4.4).

*Paediatric population*
There is no relevant use of enzalutamide in the paediatric population in the indication of treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

Method of administration
Xtandi is for oral use. The capsules should be swallowed whole with water, and can be taken with or without food.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Women who are or may become pregnant (see section 4.6).

## 4.4 Special warnings and precautions for use

Risk of seizure
Caution should be used in administering Xtandi to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold.

Concomitant use with other medicinal products
Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products (see examples in section 4.5). A review of concomitant medicinal products should therefore be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters (see section 4.5) should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If Xtandi is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted (see section 4.5).

Renal impairment
Caution is required in patients with severe renal impairment as enzalutamide has not been studied in this patient population.

Hepatic impairment
Caution is required in patients with moderate hepatic impairment (Child-Pugh Class B) as data in moderate hepatic impairment are not fully conclusive (see section 5.2). As there are no data in patients with severe hepatic impairment and enzalutamide is primarily hepatically eliminated, Xtandi is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).

Recent cardiovascular disease
The AFFIRM study excluded patients with recent myocardial infarction (in the past 6 months) or unstable angina (in the past 3 months), New York Heart Association Class (NYHA) III or IV heart failure except if Left Ventricular Ejection Fraction (LVEF) ≥ 45%, long QT, QTcF > 470 ms, bradycardia or uncontrolled hypertension. This should be taken into account if Xtandi is prescribed in these patients.

Use with chemotherapy
The safety and efficacy of concomitant use of Xtandi with cytotoxic chemotherapy has not been established.

Excipients
Xtandi contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

## 4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect enzalutamide exposures

*CYP2C8 inhibitors and inducers*
CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects, the AUC of enzalutamide increased by 326% while $C_{max}$ of enzalutamide decreased by 18%. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 77% while $C_{max}$ decreased by 19%. Strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily (see section 4.2).

*CYP3A4 inhibitors and inducers*
CYP3A4 plays a minor role in the metabolism of enzalutamide. Following oral administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily) to healthy male subjects, the AUC of enzalutamide increased by 41% while $C_{max}$ was unchanged. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 27% while $C_{max}$ was again unchanged. No dose adjustment is necessary when Xtandi is co-administered with inhibitors or inducers of CYP3A4.

Potential for enzalutamide to affect exposures to other medicinal products

*Enzyme induction*
Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites. Enzymes that may be induced include CYP3A in the liver and gut, CYP2C9, CYP2C19, CYP1A2 and uridine 5'-diphospho-glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). The transport protein P-gp may also be induced, and probably other transporters as well, e.g. multidrug resistance-associated protein 2 (MRP2), breast cancer resistant protein (BCRP) and the organic anion transporting polypeptide 1B1 (OATP1B1).

In vivo studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of enzalutamide (160 mg once daily) with single oral doses of sensitive CYP substrates in prostate cancer patients resulted in an 86% decrease in the AUC of midazolam (CYP3A4 substrate), a 56% decrease in the AUC of S-warfarin (CYP2C9 substrate), and a 70% decrease in the AUC of omeprazole (CYP2C19 substrate). UGT1A1 may have been induced as well.

Interactions with certain medicinal products that are eliminated through metabolism or active transport are expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

Groups of medicinal products that can be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, tramadol)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. acenocoumarol, warfarin)
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Betablockers (e.g. bisoprolol, propanolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- Corticosteroids (e.g. dexamethasone, prednisolone)
- HIV antivirals (e.g. indinavir, ritonavir)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Statins metabolized by CYP3A4 (e.g. atorvastatine, simvastatin)
- Thyroid agents (e.g. levothyroxine)

The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Patients taking medicinal products that are substrates of CYP3A4, CYP2C9, CYP2C19, CYP1A2 or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment, and dose adjustment should be considered as appropriate. In consideration of the long half-life of enzalutamide (5.8 days, see section 5.2), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping enzalutamide treatment.

*CYP2C8 substrates*
Enzalutamide (160 mg once daily) did not cause a clinically relevant change in the AUC or $C_{max}$ of pioglitazone (CYP2C8 substrate). The AUC of pioglitazone increased by 20% while $C_{max}$ decreased by 18%. No dose adjustment is indicated when a CYP2C8 substrate is co-administered with Xtandi.

*P-gp substrates*
*In vitro* data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. The effect of enzalutamide on P-gp substrates has not been evaluated *in vivo*; however, under conditions of clinical use, enzalutamide may be an inducer of P-gp via activation of the nuclear pregnane receptor (PXR). Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with Xtandi and may require dose adjustment to maintain optimal plasma concentrations.

*BCRP, MRP2, OAT3 and OCT1 substrates*
Based on in vitro data, inhibition of BCRP and MRP2 (in the intestine), as well as organic anion transporter 3 (OAT3) and organic cation transporter 1 (OCT1) (systemically) cannot be excluded. Theoretically, induction of these transporters is also possible, and the net effect is presently unknown.

Effect of food on enzalutamide exposures
Food has no clinically significant effect on the extent of exposure to enzalutamide. In clinical trials, Xtandi was administered without regard to food.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential
There are no human data on the use of Xtandi in pregnancy and this medicinal product is not for use in women of childbearing potential.

Contraception in males and females
It is not known whether enzalutamide or its metabolites are present in semen. A condom is required during and for 3 months after treatment with enzalutamide if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential, a condom and another form of birth control must be used during and for 3 months after treatment. Studies in animals have shown reproductive toxicity (see section 5.3).

Pregnancy
Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant (see sections 4.3 and 5.3).

Breast-feeding
Enzalutamide is not for use in women.

Fertility
Animal studies showed that enzalutamide affected the reproductive system in male rats and dogs (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Enzalutamide may have a moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizures have been reported (see section 4.8). Patients with a history of seizures or other predisposing factors (see section 4.4) should be advised of the risk of driving or operating machines. No studies to establish the effects of enzalutamide on the ability to drive and use machines have been conducted.

## 4.8 Undesirable effects

Summary of the safety profile
In the placebo-controlled phase 3 clinical trial (AFFIRM) of patients with metastatic castration-resistant prostate cancer who had received docetaxel therapy, enzalutamide was administered at a dose of 160 mg daily (N = 800) versus placebo (N = 399). The median duration of treatment with enzalutamide was 8.3 months while with placebo it was 3.0 months. Patients were allowed, but not required, to take prednisone.

Seizure occurred in 0.8% of patients receiving enzalutamide. The most common adverse reactions were hot flush and headache.

Tabulated summary of adverse reactions
Adverse reactions in AFFIRM are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 1: Adverse reactions identified in the phase 3 clinical trial**

| MedDRA System organ class | very common | common | uncommon |
|---|---|---|---|
| Blood and lymphatic system disorders | | neutropenia | leucopenia |
| Psychiatric disorders | | visual hallucinations<br>anxiety | |
| Nervous system disorders | headache | cognitive disorder<br>memory impairment | seizure<br>amnesia<br>disturbance in attention |
| Vascular disorders | hot flush | hypertension | |
| Skin and subcutaneous tissue disorders | | dry skin<br>pruritus | |
| Musculoskeletal and connective tissue disorders | | fractures* | |
| Injury, poisoning and procedural complications | | falls | |

* Includes all fractures with the exception of pathological fractures

Description of selected adverse reactions

*Seizures*
In AFFIRM, six patients (0.8%) experienced a seizure out of 800 patients treated with a daily dose of 160 mg enzalutamide, whereas no seizures occurred in patients receiving placebo. Potentially contributing factors were present in several of these patients that may have independently increased their risk of seizure. The AFFIRM trial excluded patients with prior seizure or risk factors for seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose-escalation study. The mechanism by which enzalutamide may lower the seizure threshold is not known, but could be related to data from *in vitro* studies showing that enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA-gated chloride channel.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no antidote for enzalutamide. In the event of an overdose, treatment with enzalutamide should be stopped and general supportive measures initiated taking into consideration the half-life of 5.8 days. Patients may be at increased risk of seizures following an overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned, ATC code: not yet assigned

Mechanism of action
Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signalling. Despite low or even undetectable levels of serum androgen, androgen receptor signalling continues to promote disease progression. Stimulation of tumour cell growth via the androgen receptor requires nuclear localization and DNA binding. Enzalutamide is a potent androgen receptor signalling

inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits binding of androgens to androgen receptors, inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. In preclinical studies enzalutamide lacks androgen receptor agonist activity.

Pharmacodynamic effects

In a phase 3 clinical trial of patients who failed prior chemotherapy with docetaxel, 54% of patients treated with enzalutamide, versus 1.5% of patients who received placebo, had at least a 50% decline from baseline in PSA levels.

Clinical efficacy and safety

The efficacy and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer who had received docetaxel and were using a gonadotropin-releasing hormone (GnRH) analogue or had undergone orchiectomy were assessed in a randomised, placebo-controlled, multicentre phase 3 clinical trial. A total of 1199 patients were randomised 2:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 800) or placebo once daily (N = 399). Patients were allowed but not required to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent). Patients randomised to either arm were to continue treatment until disease progression (defined as confirmed radiographic progression or the occurrence of a skeletal-related event) and initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41-92) and the racial distribution was 92.7% Caucasian, 3.9% Black, 1.1% Asian, and 2.1% Other. The ECOG performance score was 0-1 in 91.5% of patients and 2 in 8.5% of patients; 28.4% had a mean Brief Pain Inventory score of ≥4 (mean of patient's reported worst pain over the previous 24 hours calculated for seven days prior to randomization). Most (91.2%) patients had metastases in bone and 23.2% had visceral lung and/or liver involvement. At study entry, 41% of randomized patients had PSA progression only, whereas 59% of patients had radiographic progression. 51% of patients were on bisphosphonates at baseline.

The phase 3 study excluded patients with medical conditions that may predispose them to seizures (see section 4.8) and medicinal products known to decrease the seizure threshold, as well as clinically significant cardiovascular disease such as uncontrolled hypertension, recent history of myocardial infarction or unstable angina, New York Heart Association class III or IV heart failure (unless ejection fraction was ≥ 45%), clinically significant ventricular arrhythmias or AV block (without permanent pacemaker).

Of the 800 patients in the phase 3 trial who received enzalutamide, 568 patients (71%) were 65 years and over and 199 patients (25%) were 75 years and over. No overall differences in safety or effectiveness were observed between these older patients and younger patients.

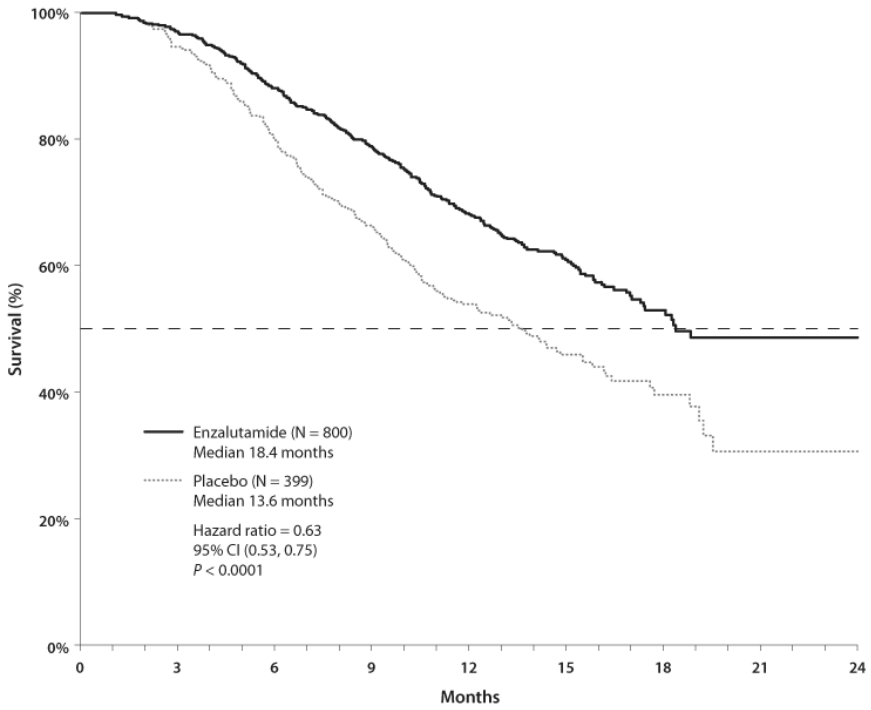
The protocol pre-specified interim analysis after 520 deaths showed a statistically significant superiority in overall survival in patients treated with enzalutamide compared to placebo (Table 2 and Figure 1).

**Table 2: Overall survival of patients treated with either enzalutamide or placebo (intent-to-treat analysis)**

| | **Enzalutamide (N = 800)** | **Placebo (N = 399)** |
|---|---|---|
| Deaths (%) | 308 (38.5%) | 212 (53.1%) |
| Median survival (months) (95% CI) | 18.4 (17.3, NR) | 13.6 (11.3, 15.8) |
| p value[a] | < 0.0001 | |
| Hazard ratio (95% CI)[b] | 0.631 (0.529, 0.752) | |

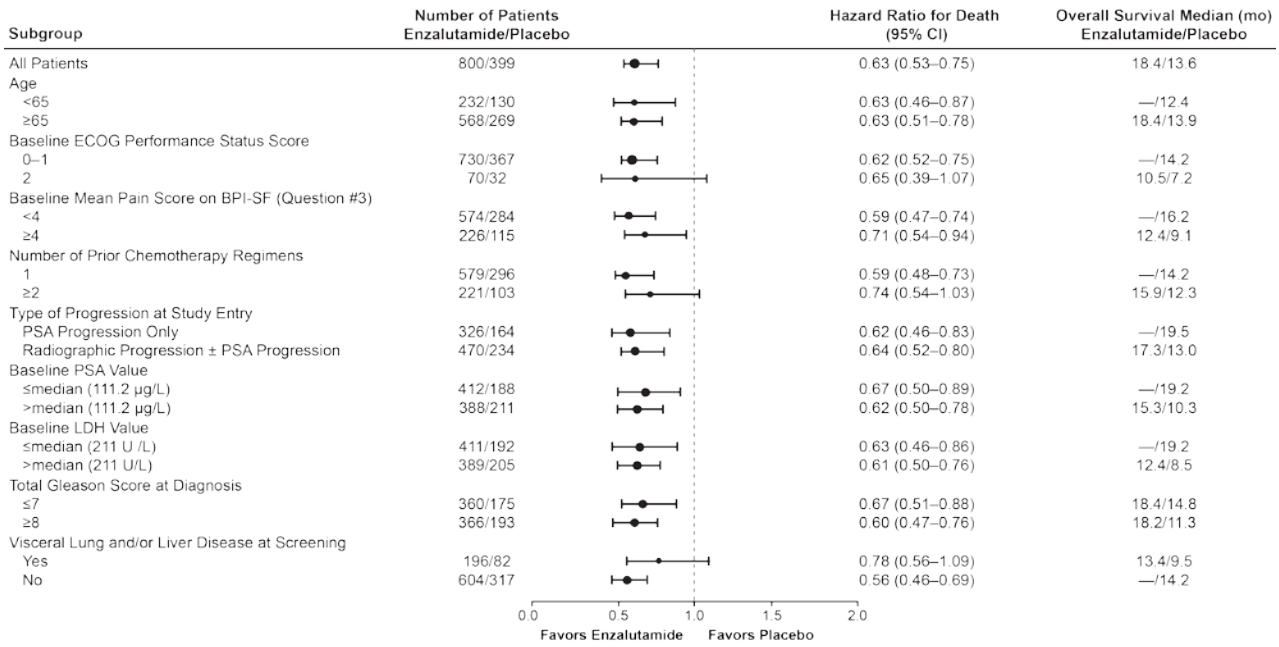
[a] P-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2) and mean pain score (< 4 vs. ≥ 4)
[b] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio < 1 favours enzalutamide

**Figure 1: Kaplan-Meier Overall Survival Curves (Intent-to-Treat Analysis)**




Subgroup survival analysis showed a consistent survival benefit for treatment with enzalutamide (see Figure 2)

**Figure 2: Overall Survival by Subgroup – Hazard Ratio and 95% Confidence Interval**




ECOG: Eastern Cooperative Oncology Group; BPI-SF: Brief Pain Inventory-Short Form; PSA: Prostate Specific Antigen

In addition to the observed improvement in overall survival, key secondary endpoints (PSA progression, radiographic progression-free survival, and time to first skeletal-related event) favoured enzalutamide and were statistically significant after adjusting for multiple testing.

Radiographic progression-free survival as assessed by the investigator using RECIST v1.1 for soft tissue and appearance of 2 or more bone lesions in bone scan was 8.3 months for patients treated with enzalutamide and 2.9 months for patients who received placebo (HR = 0.404, 95% CI: [0.350, 0.466]); $p < 0.0001$). The analysis involved 216 deaths without documented progression and 645 documented progression events, of which 303 (47%) were due to soft tissue progression, 268 (42%) were due to bone lesion progression and 74 (11%) were due to both soft tissue and bone lesions.

Confirmed PSA decline of 50% or 90% were 54.0% and 24.8%, respectively, for patients treated with enzalutamide and 1.5% and 0.9%, respectively, for patients who received placebo ($p < 0.0001$). The median time to PSA progression was 8.3 months for patients treated with enzalutamide and 3.0 months for patients who received placebo (HR = 0.248, 95% CI: [0.204, 0.303]; $p < 0.0001$).

The median time to first skeletal-related event was 16.7 months for patients treated with enzalutamide and 13.3 months for patients who received placebo (HR = 0.688, 95% CI: [0.566, 0.835]; $p < 0.0001$). A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. The analysis involved 448 skeletal-related events, of which 277 events (62%) were radiation to bone, 95 events (21%) were spinal cord compression, 47 events (10%) were pathologic bone fracture, 36 events (8%) were change in anti-neoplastic therapy to treat bone pain and 7 events (2%) were surgery to bone.

The efficacy of enzalutamide in patients who have previously received abiraterone acetate has not been studied.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with enzalutamide in all subsets of the paediatric population in prostate carcinoma (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Enzalutamide is poorly water soluble. In this product, the solubility of enzalutamide is increased by caprylocaproyl macrogolglycerides as emulsifier/surfactant. In preclinical studies, the absorption of enzalutamide was increased when dissolved in caprylocaproyl macrogolglycerides.

The pharmacokinetics of enzalutamide have been evaluated in prostate cancer patients and in healthy male subjects. The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days), and steady state is achieved in approximately one month. With daily oral administration, enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in plasma concentrations are low (peak-to-trough ratio of 1.25). Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite that is equally as active as enzalutamide and circulates at approximately the same plasma concentration as enzalutamide.

Absorption
Maximum plasma concentrations ($C_{max}$) of enzalutamide in patients are observed 1 to 2 hours after administration. Based on a mass balance study in humans, oral absorption of enzalutamide is estimated to be at least 84.2%. Enzalutamide is not a substrate of the efflux transporters P-gp or BCRP. At steady state, the mean $C_{max}$ values for enzalutamide and its active metabolite are 16.6 μg/mL (23% coefficient of variation [CV]) and 12.7 μg/mL (30 %CV), respectively.

Food has no clinically significant effect on the extent of absorption. In clinical trials, Xtandi was administered without regard to food.

Distribution
The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV). The volume of distribution of enzalutamide is greater than the volume of total body water, indicative of extensive extravascular distribution. Studies in rodents indicate that enzalutamide and its active metabolite can cross the blood brain barrier.

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. The active metabolite is 95% bound to plasma proteins.

Biotransformation
Enzalutamide is extensively metabolized. There are two major metabolites in human plasma: N-desmethyl enzalutamide (active) and a carboxylic acid derivative (inactive). Enzalutamide is metabolized by CYP2C8 and to a lesser extent by CYP3A4/5 (see section 4.5), both of which play a role in the formation of the active metabolite.

Under conditions of clinical use, enzalutamide is a strong inducer of CYP3A4, a moderate inducer of CYP2C9 and CYP2C19, and has no clinically relevant effect on CYP2C8 (see section 4.5).

Elimination
The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0.520 and 0.564 L/h.

Following oral administration of $^{14}$C-enzalutamide, 84.6% of the radioactivity is recovered by 77 days post dose: 71.0% is recovered in urine (primarily as the inactive metabolite, with trace amounts of enzalutamide and the active metabolite), and 13.6% is recovered in faeces (0.39% of dose as unchanged enzalutamide).

*In vitro* data indicate that enzalutamide is not a substrate for OATP1B1, OATP1B3, or OCT1.

*In vitro* data indicate that enzalutamide and its major metabolites do not inhibit the following transporters at clinically relevant concentrations: OATP1B1, OATP1B3, OCT2, or OAT1.

Linearity
No major deviations from dose proportionality are observed over the dose range 40 to 160 mg. The steady-state $C_{min}$ values of enzalutamide and the active metabolite in individual patients remained constant during more than one year of chronic therapy, demonstrating time-linear pharmacokinetics once steady-state is achieved.

Renal impairment
No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177 μmol/L (2 mg/dL) were excluded from clinical trials. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for patients with calculated creatinine clearance (CrCL) values ≥ 30 mL/min (estimated by the Cockcroft and Gault formula). Enzalutamide has not been evaluated in patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease, and caution is advised when treating these patients. It is unlikely that enzalutamide will be significantly removed by intermittent haemodialysis or continuous ambulatory peritoneal dialysis.

Hepatic impairment
The pharmacokinetics of enzalutamide were examined in subjects with baseline mild (N = 6) or moderate (N = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 14 matched control subjects with normal hepatic function. Following a single oral 160 mg dose of enzalutamide, the AUC and $C_{max}$ for enzalutamide in subjects with mild impairment increased by 5% and 24%, respectively, and the AUC and $C_{max}$ of enzalutamide in subjects with moderate impairment increased by 29% and decreased by 11%, respectively, compared to healthy control subjects. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC and $C_{max}$ in subjects with mild impairment increased by 14% and 19%, respectively, and the AUC and $C_{max}$ in subjects with moderate impairment increased by 14% and decreased by 17%, respectively, compared to healthy control subjects. The patients in the moderate hepatic impairment group however had only modest impairment in parameters indicative of metabolic function (albumin, prothrombin time), and thus a larger effect in other patients with moderate hepatic impairment cannot be excluded.

Patients with baseline severe hepatic impairment (Child-Pugh C) were excluded from clinical trials.

Race
Most patients in the clinical trials (> 92%) were Caucasian, thus no conclusions on the impact of race on enzalutamide pharmacokinetics can be drawn.

Older people
No clinically relevant effect of age on enzalutamide pharmacokinetics was seen in the population pharmacokinetic analysis.

## 5.3 Preclinical safety data

Developmental or reproductive toxicology studies were not conducted with enzalutamide, but in studies in rats (4 and 26 weeks) and dogs (4 and 13 weeks), atrophy, aspermia/hypospermia, and hypertrophy/hyperplasia in the reproductive system were noted, consistent with the pharmacological activity of enzalutamide. In studies in rats (4 and 26 weeks) and dogs (4 and 13 weeks), changes in the reproductive organs associated with enzalutamide were decreases in organ weight with atrophy of the prostate and epididymis. Additional changes to reproductive tissues included hypertrophy/hyperplasia of the pituitary gland and atrophy in seminal vesicles in rats and testicular hypospermia and seminiferous tubule degeneration in dogs. Gender differences were noted in rat mammary glands (male atrophy and female lobular hyperplasia). Changes in the reproductive organs in both species were consistent with the pharmacological activity of enzalutamide and reversed or partially resolved after an 8-week recovery period. There were no other important changes in clinical pathology or histopathology in any other organ system, including the liver, in either species.

Enzalutamide did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in either the *in vitro* cytogenetic assay with mouse lymphoma cells or the *in vivo* mouse

micronucleus assay. Long-term animal studies to evaluate the carcinogenic potential of enzalutamide have not been conducted. Enzalutamide was not phototoxic *in vitro*.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule contents
Caprylocaproyl macrogol-8 glycerides
Butylhydroxyanisole (E320)
Butylhydroxytoluene (E321)

Capsule shell
Gelatin
Sorbitol sorbitan solution
Glycerol
Titanium dioxide (E171)
Purified water

Printing ink
Iron oxide black (E172)
Polyvinyl acetate phthalate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Cardboard wallet incorporating a PVC/PCTFE/aluminium blister of 28 soft capsules. Each carton contains 4 wallets (112 soft capsules).

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/H/13/846/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON WITH BLUE BOX**

## 1. NAME OF THE MEDICINAL PRODUCT

Xtandi 40 mg soft capsules
enzalutamide

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg enzalutamide.

## 3. LIST OF EXCIPIENTS

Contains sorbitol (E420).
See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

112 soft capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/H/13/846/001 112 soft capsules

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

xtandi 40 mg

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**WALLET WITHOUT BLUE BOX**

## 1. NAME OF THE MEDICINAL PRODUCT

Xtandi 40 mg soft capsules
enzalutamide

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg enzalutamide.

## 3. LIST OF EXCIPIENTS

Contains sorbitol (E420).
See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

28 soft capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

xtandi 40 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Xtandi 40 mg

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Xtandi 40 mg soft capsules**
enzalutamide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Xtandi is and what it is used for

Xtandi contains the active substance enzalutamide. Xtandi is used to treat adult men with prostate cancer that has spread to other parts of the body after they have received chemotherapy.

**How Xtandi works**
Xtandi is a medicine that works by blocking the activity of hormones called androgens (such as testosterone). By blocking androgens, enzalutamide stops prostate cancer cells from growing and dividing.

## 2. What you need to know before you take Xtandi

**Do not take Xtandi:**
- If you are allergic (hypersensitive) to enzalutamide or any of the other ingredients of this medicine (listed in section 6).
- If you are pregnant or may become pregnant (see 'Pregnancy, breast-feeding and fertility')

**Warnings and precautions**
Seizures
Seizures have been reported in about 7 or 8 in every 1,000 people taking Xtandi (see also 'Other medicines and Xtandi' in this section and section 4 'Possible side effects').
Some situations in which you may have a higher risk of seizures include:
- If you had earlier episodes of seizures
- If you have had a serious head injury or a history of head trauma
- If you have had certain kinds of stroke
- If you have had a brain tumour or cancer which has spread to the brain
- If you drink very large amounts of alcohol either regularly or from time to time
- If you are taking a medicine that can cause seizures or that can increase the susceptibility for

having seizures (see ‘Other medicines and Xtandi’ below)

If you have a seizure during treatment:
Stop taking Xtandi and do not take any more capsules. See your doctor as soon as possible.

Talk to your doctor before taking Xtandi
- If you are taking any medicines to prevent blood clots (e.g. warfarin, acenocoumarol)
- If you have problems with your liver
- If you have problems with your kidneys

**If any of the above applies to you or you are not sure, talk to your doctor before taking this medicine.**

**Children and adolescents**
This medicine is not for use in children and adolescents.

**Other medicines and Xtandi**
Tell your doctor if you are taking, have recently taken or might take any other medicines. You need to know the names of the medicines you take. Keep a list of them with you to show to your doctor when you are prescribed a new medicine. You should not start or stop taking any medicine before you talk with the doctor that prescribed Xtandi.

Tell your doctor if you are taking any of the following medicines. When taken at the same time as Xtandi, these medicines may increase the risk of a seizure:

- Certain medicines used to treat asthma and other respiratory diseases (e.g. aminophylline, theophylline)
- Medicines used to treat certain psychiatric disorders such as depression and schizophrenia (e.g. clozapine, olanzapine, risperidone, ziprasidone, bupropion, lithium, chlorpromazine, mesoridazine, thioridazine, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
- Certain medicines for the treatment of pain (e.g. pethidine)

Tell your doctor if you are taking the following medicines. These medicines may influence the effect of Xtandi, or Xtandi may influence the effect of these medicines:

This includes certain medicines used to:
- Lower cholesterol (e.g. gemfibrozil, atorvastatin, simvastatin)
- Treat pain (e.g. fentanyl, tramadol)
- Treat cancer (e.g. cabazitaxel)
- Treat epilepsy (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Treat certain psychiatric disorders such as severe anxiety or schizophrenia (e.g. diazepam, midazolam, haloperidol)
- Treat sleep disorders (e.g. zolpidem)
- Treat heart conditions or lower blood pressure (e.g. bisoprolol, digoxin, diltiazem, felodipine, nicardipine, nifedipine, propanolol, verapamil)
- Treat serious disease related to inflammation (e.g. dexamethasone, prednisolone)
- Treat HIV infection (e.g. indinavir, ritonavir)
- Treat bacterial infections (e.g. clarithromycin, doxycycline, rifampicin)
- Treat thyroid disorders (e.g. levothyroxine)
- Treat gout (e.g. colchicine)
- Prevent heart conditions or strokes (dabigatran etexilate)

Tell your doctor if you are taking any of the medicines listed above. The dose of Xtandi or any other medicines that you are taking may need to be changed.

**Pregnancy, breast-feeding and fertility**
- **Xtandi is not for use in women.** This medicine may cause harm to the unborn child if it is taken by women who are pregnant. It must not be taken by women who are pregnant, may become pregnant, or who are breast-feeding.
- This medicine could possibly have an effect on male fertility.
- If you are having sex with a woman who can become pregnant, use a condom and another effective birth control method, during treatment and for 3 months after treatment with this medicine. If you are having sex with a pregnant woman, use a condom to protect the unborn child.

**Driving and using machines**
This medicine may have a moderate effect on your ability to drive or use any tools or machines as the side effects for Xtandi include seizures. If you are at higher risk of seizures (see Section 2), talk to your doctor.

**Xtandi contains sorbitol**
This medicine contains sorbitol (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Xtandi

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The usual dose is 160 mg (four capsules), taken at the same time once a day.

**Taking Xtandi**
- Swallow the capsules whole with water.
- Do not chew, dissolve or open the capsules before swallowing.
- Xtandi can be taken with or without food.

**If you take more Xtandi than you should**
If you take more capsules than prescribed, stop taking Xtandi and contact your doctor. You may have an increased risk of seizure or other side effects.

**If you forget to take Xtandi**
- If you forget to take Xtandi at the usual time, take your usual dose as soon as you remember.
- If you forget to take Xtandi for the whole day, take your usual dose the following day.
- If you forget to take Xtandi for more than one day, talk to your doctor immediately.
- **Do not take a double dose** to make up for the dose you forgot.

**If you stop taking Xtandi**
Do not stop taking this medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Seizures**
Seizures have been reported in about 7 or 8 in every 1,000 people taking Xtandi.
Seizures are more likely if you take more than the recommended dose of this medicine, if you take certain other medicines, or if you are at higher than usual risk of seizures (see section 2).

**If you have a seizure**, see your doctor as soon as possible. Do not take any more Xtandi.

Other possible side effects include:

**Very common** (may affect more than 1 in 10 people)
- Headache
- Hot flushes

**Common** (may affect up to 1 in 10 people)
- Falls
- Broken bones
- Hallucinations
- Feeling anxious
- Dry skin
- Itching
- High blood pressure
- Low white blood cell count
- Difficulty remembering
- Difficulty thinking clearly

**Uncommon (**may affect up to 1 in 100 people**)**
- Forgetfulness
- Reduced concentration

**Reporting of side effects**
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Xtandi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the cardboard wallet and outer carton. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not take any capsule that is leaking, damaged, or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Xtandi contains**
- The active substance is enzalutamide. Each capsule contains 40 mg of enzalutamide.
- The other ingredients of the capsule are caprylocaproyl macrogol-8 glycerides, butylhydroxyanisole (E320), and butylhydroxytoluene (E321).
- The ingredients of the capsule shell are gelatin, sorbitol sorbitan solution (see section 2), glycerol, titanium dioxide (E171), and purified water.
- The ingredients of the ink are iron oxide black (E172) and polyvinyl acetate phthalate.

**What Xtandi looks like and contents of the pack**

- Xtandi capsules are white to off-white, oblong soft capsules (approximately 20 mm by 9 mm) with “ENZ” written on one side.
- Each carton contains 112 capsules in 4 blister wallets of 28 capsules each.

**Marketing Authorisation Holder and Manufacturer**

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.